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(74) Agents: FLORENCE, Julia, Anne et al.; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).

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(71) Applicant *(for all designated States except US)*: ALIZYME THERAPEUTICS LIMITED [GB/GB]; Granta Park, Great Abingdon, Cambridge CB1 6GS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HODSON, Harold, Francis [GB/GB]; 69 Whitecroft Way, Beckenham, Kent BR3 3AW (GB). DOWNHAM, Robert [GB/GB]; Cambridge Discovery Chemistry, The Merrifield Centre, Rosemary Lane, Cambridge CB1 3LQ (GB). MITCHELL, Timothy, John [GB/GB]; Cambridge Discovery Chemistry, The Merrifield Centre, Rosemary Lane, Cambridge CB1 3LQ (GB). CARR, Beverley, Jane [GB/GB]; Boys Bridge Cottage, Fen Road, Abbington Piggotts, Cambs. SG8 5PQ (GB). DUNK, Christopher, Robert [GB/GB]; Alizyme Therapeutics Limited, 280 Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). PALMER, Richard, Michael, John [GB/GB]; Alizyme Therapeutics Limited, 280 Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

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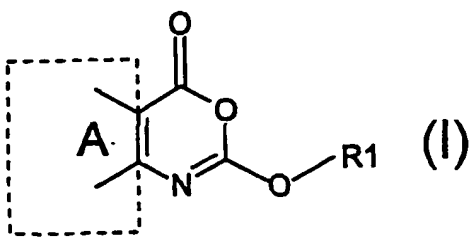

(I)

(57) Abstract: The use of a compound comprising formula (I) or a salt, ester, amide or prodrug therof in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester functionality, e.g. in the control and inhibition of unwanted enzymes in products and processes. The compounds are also useful in medicine e.g. in the treatment of obesity and related conditions. The invention also relates to novel compounds within formula (I), to processes for preparing them and pharmaceutical compositions containing them. In formula (I) A is a 6-membered aromatic or heteroaromatic ring; and R^1 is a branched or unbranched alkyl (optionally interrupted by one or more oxygen atoms), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, reduced aryl, reduced heteroaryl, reduced heteroarylalkyl or a substituted derivative of any of the foregoing groups.

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00576874 **Image available**

2-AMINO-4H-3,1-BENZOXAZIN-4-ONE DERIVATIVES FOR THE TREATMENT OF OBESITY

2-AMINO-4H-3,1-BENZOXAZINE-4-ONES DESTINEES AU TRAITEMENT DE L'OBESITE

Patent Applicant/Assignee:
ALIZYME THERAPEUTICS LIMITED,
HODSON Harold Francis,
DOWNHAM Robert,
MITCHELL Timothy John,
CARR Beverley Jane,
DUNK Christopher Robert,
PALMER Richard Michael John,
Inventor(s):
HODSON Harold Francis,
DOWNHAM Robert,
MITCHELL Timothy John,
CARR Beverley Jane,
DUNK Christopher Robert,
PALMER Richard Michael John,

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English Abstract

The use of a compound comprising formula (I) or a salt, ester, amide or prodrug therof in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester functionality, e.g. in the control and inhibition of unwanted enzymes in products and processes. The compounds are also useful in medicine e.g. in the treatment of obesity and related conditions. The invention also relates to novel compounds within formula (I), to processes for preparing them and pharmaceutical compositions containing them. In formula (I) A is a 6-membered aromatic or heteroaromatic ring; and R1 is a branched or unbranched alkyl (optionally interrupted by one or more oxygen atoms), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, reduced aryl, reduced heteroaryl, reduced

heteroarylalkyl or a substituted derivative of any of the foregoing groups.

French Abstract

L'invention concerne l'utilisation d'un compose de formule (I) ou d'un sel, d'un ester, d'un amide ou d'un promedicament dudit compose, pour inhiber une enzyme dont le mode d'action prefere est de catalyser l'hydrolyse d'une fonctionnalite ester, par exemple pour la regulation et l'inhibition des enzymes indesirables dans les produits et les processus. Ces composes sont egalement utiles en medecine, par exemple pour le traitement de l'obesite et des pathologies voisines. L'invention concerne egalement des composes de formule (I), des procedes permettant de les preparer et des compositions pharmaceutiques les contenant. Dans la formule (I) A est un noyau aromatique ou hetero-aromatique a 6 elements; et R1 est alkyle ramifie ou non ramifie (eventuellement interrompu par un ou plusieurs atomes d'oxygene), alcenyle, alcinyle, cycloalkyle, cycloalcenyle, aryle, arylalkyle, arylalkyle reduit, arylalcenyle, heteroaryle, hetero-arylalkyle, hetero-arylalcenyle, aryle reduit, hetero-aryle reduit, hetero-arylalkyle reduit, ou un derive substitue de l'un des groupes ci-dessus.

Detailed Description

-AM1N0-4H-3t1-BENZOXAZ1N ONE DERIVATIVES FOR THE TREATMENT OF OBESrry

The present invention provides known and novel compounds, their use in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester functionality (in vivo, as the enzyme naturally occurs), their use in medicine, and particularly in the prevention and/or treatment of obesity or an obesityrelated disorder. Also provided are methods for the prevention and/or treatment of obesity or an obesity-related disorder and for promoting/ aiding non-medical weight loss and the use of the compounds in the manufacture of a medicament for the I 0 aforementioned indications. In respect of novel compounds the invention also provides processes for their manufacture, compositions containing them, and methods for manufacturing such compositions.

In the last 20 years, there has been an increasing trend in obesity in the populations of 1 5 the developed world. The increased incidence of obesity is due in part to the ready availability of food in numerous retail outlets and westemised diets that have high saturated fat and lower fibre contents such that the food is energy dense. The lifestyle of the populations of the developed world has also become more sedentary with the increased mechanisation of society and the steady reduction of manual labour intensive industries. There now exists an energy imbalance between the energy intake from calorie dense foods and the reduced energy expenditure required for a sedentary lifestyle. Some of the excess energy intake is stored as fat in the adipose tissue, the accumulation of which over a period of time results in obesity and can be a significant contributory factor to other diseases and disorders.

Obesity is now recognised by the medical profession as a metabolic disease. In the USA, it is estimated that 25% of the adult population is considered clinically obese (Body Mass Index>30). Obesity can be a debilitating condition which reduces the quality of life and increases the risk of related disorders such as diabetes, cardiovascular disease and hypertension. It has been estimated that $45 billion of US healthcare costs, or 8% per annum of total healthcare spend, is as a direct result of obesity. The traditional approaches to long term weight management such as diet and exercise have proved ineffective alone to control the spread of obesity. Today, more than ever, there is considerable interest in developing safe, effective drugs for the treatment of obesity.

Pharmacological approaches to the treatment of obesity have focused on either developing drugs

that increase energy expenditure or drugs that reduce energy intake.

One approach to the reduction of energy intake is to reduce the body's ability to digest and absorb food, in particular fat. The key enzymes involved in the digestion of fat are hydrolytic enzymes. The most significant of the fat degrading enzymes are lipases, primarily, but not exclusively pancreatic lipase that is secreted by the pancreas into the gut lumen. The lipase inhibitor lipstatin has formed the basis of the anti-obesity drug, orlistat. Orlistat is the subject of published European Patent Application No.

EP129748, which relates to compounds of formula.

NC
0
A
where A is -(CH2)5- or.

H H
and their use in inhibiting pancreatic lipase and treating hyperlipaernia and obesity.

Orlistat has as its major active moiety a beta-lactone group that reacts to form an ester with the side chain hydroxyl group of serine 152 within the active site of pancreatic lipase. Even if orlistat provides an effective method for treating obesity, there remains a need to provide alternative drugs and methods for use in the control and treatment of obesity, obesity-related disorders and non-medical weight loss. Inhibitors of enzymes I 0 involved in the degradation of fat are provided here and shown to be effective in the prevention and/or treatment of obesity, obesity-related disease and/or cosmetic weight loss.

US Patent No. 4,657,893 (Syntex) describes a broad class of 2-amino-4H-3,1 1 5 benzoxazin ones of the formula.

R1 0
0
R2 W@x
R3
wherein R' is hydrogen or lower alkyl, R@ and W are each independently hydrogen, halo, lower alkyl, hydroxy, lower alkoxy, lower thioalkyl, -NO2, -N(R')2, -NR'COR', -NHCON(R')2 or NHCOOR'; and X is inter alia -NHR where R is lower alkyl, lower alkenyl, lower alkynyl, optionally substituted lower cycloalkyl or optionally substituted phenyl lower alkyl. The compounds are said to be useful as serine protease inhibitors and to treat physiologic conditions and disease states known to involve serine proteases, or as contraceptives. The specification describes various conditions and diseases involving enzymatic pathways, including inflammation, arthritis, tumor cell metastasis, pulmonary emphysema, mucocutaneous lymph node syndrome, adult respiratory distress syndrome and pancreatitis. It is also suggested that the compounds may have antiparasitic, anticoagulant and/or antiviral activity. Similar compounds are
also described by Krantz et al in J Med Chem. 1990 33:464
2-Amino-4H-3,1-benzoxazin ones as inhibitors of serine protease are also described by Hays et al in J Med Chem. 1998 41:1060 This paper describes inter alia 2(substituted phenyl)amino benzoxazinones, where the phenyl substituents include
halogen, methyl, SMe, and OCF3, as well as certain 2-(heterocyclic)amino
benzoxazinones. Some of these compounds are also described in US Patent No.

I 0 5,652,237 (Warner Lambert).

German OLS 2315303 (Bayer AG) describes the preparation of compounds of the formula
R' 0
0
N-:@ N R
R"
where R is an alkyl or aryl residue which may be substituted by nitro, halogen, alkyl, alkoxy or an aryl group, and R' and R" are each independently hydrogen, halogen, nitro, optionally substituted alkyl, cycloalkyl, aralkyl, aryl, alkoxy or aryloxy groups.

The only values of R exemplified are nitrophenyl and mono- and di-chlorophenyl.

The compounds are said to be useful as intermediates for pharmaceuticals and plant protection agents.

We have now found that a particular class of benzoxazinone compounds has activity as lipase inhibitors
Accordingly, a first aspect of the invention provides a compound comprising formula (I)
0
N'I"N
R2
or a pharmaceutically acceptable salt, ester, amide or prodrug therof; in the manufacture of a medicament for the treatment of conditions which require the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester functionality; wherein in formula (I).

1 0 A is a 6 membered aromatic or hetero-aromatic ring;
R' is a branched or unbranched alkyl (optionally interrupted by one or more oxygen atoms), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, reduced aryl, reduced 1 5 heteroaryl, reduced heteroarylalkyl or a substituted derivative therof wherein the substituents are one or more independently chosen from the group consisting of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, heteroaryl, reduced heteroaryl,
4
reduced heteroarylalkyl, arylalkoxy, cyano, nitro, -C(O)W, -CO21e, -SOR @ -SO2W
NR6R7, -OR6, -SR6. -C(O)CX'X2NR6k, -C(O)NIeR', -C(O)N(OR')R6, -NR6C(O)W,
-CR6(NH2)CO2R 6@ -NHCX'X2CO2R 6@ -N(OH)C(O)NR 6R7@ -N(OH)C(O)RI, NHC(O)NR 6k79 -C(O)NHNR6R', -C(O)N(OR')R6, or a lipid or steroid (natural or synthetic), with the proviso that any hetero atom substituent in R' and/or W must be separated from the exocyclic nitrogen atom by at least two carbon atoms (preferably
saturated); and
PCT/GBOO/00032 R2 is hydrogen or is a group as defined above for R1;
and where:R4 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl,
6
heteroaryl, heteroarylalkyl, reduced heteroaryl, reduced heteroarylalkyl, -OR

NHCX' X2CO2R 6or -NR 6R';
R5 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, reduced heteroaryl or reduced heteroarylalkyl; R 6and R 7are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, reduced heteroaryl, heteroarylalkyl, reduced heteroarylalkyl or -(CH2)n(OR5)m wherein n is I to 12, preferably 2 to IO, wherein in is 1-3 and R5 is most preferably C2-1 0 alkyl; and Xi and X2 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, reduced heteroaryl or reduced heteroarylalkyl.

In compounds of formula (I) any alkyl, alkenyl and alkynyl groups and moieties may be straight chain (unbranched) or branched chain. Straight chain alkyl, alkenyl and alkynyl groups or moieties may contain from I to 30 carbon atoms, eg. 1 to 25 carbon atoms, preferably I to 20 carbon atoms. Branched chain alkyl, alkenyl and alkynyl groups or moieties may contain from 1 , to 5 0 carbon atoms, preferably 1 to 3 0 carbon atoms.

Preferred values for R', R, R', R', R', Xi and X2 are as defined below for formulae (11) and (Ila). In particular, preferred values for R4, R5and R6are as defined for R 13 and preferred values of R7are as defined for R14 hereinbelow.

In this text, 'reduced', in the context of 'reduced heteroaryl' and the like means fully or partially saturated.

Aryl groups include for example optionally substituted unsaturated monocyclic or bicyclic rings of up to 12 carbon atoms, such as phenyl and naphthyl, and partially saturated bicyclic rings such as tetrahydro-naphthyl. Examples of substituents which may be present on an aryl group include one or more of halogen, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, alkyl or 1-0 alkoxy.

A heteroaryl group or moiety may be for example an optionally substituted 5- or 6membered heterocyclic aromatic ring which may contain from I to 4 heteroatoms selected from 0, N and S. The heterocyclic ring may optionally be fused to a phenyl ring. Examples of heteroaryl groups thus include furyl, thienyl, pyrrolyl, oxazolyl, oxazinyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, indolyl, indazolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzoxazinyl, quinoxalinyl, quinolinyl, quinazolinyl, cinnolinyl, benzothiazolyl, pyridopyffolyl. Suitable substituents include one or more of halogen, oxo, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, haloalkyl, alkyl or alkoxy.

A reduced heteroaryl group or moiety may be for example a fully or partially saturated derivative of the aforementioned heteroaryl groups. Examples of reduced heteroaryl groups thus include pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl and piperidinyl.

The compounds of the first aspect of the invention are useful inhibitors of enzymes involved in the degradation of fats. Preferably therefore the first aspect of the invention provides the use of a compound of formula (I) as defined hereinabove, or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, in the manufacture of a medicament for the control or treatment of obesity, or obesity-related disorders or for promoting non-medical weight loss.

Preferably, a compound for use according to the first aspect of the invention is a compound of formula (II)

R8 0
R9
0
R1
R10 R2
R11
or a pharmaceutically acceptable salt, ester, amide or prodrug therof;
wherein:
R' @ R15 R'@ R5 R'@ Xi and X2 are as defined above for formula 1;
1 5
R2 is hydrogen or is a group as defined above for R'; and
R', R, Rio, R" are each independently hydrogen, halo, hydroxy, amino, nitro, cyano,
or a group R, as defined above;
or a group R12Q Where Q is O@ Co, CONH, NHCO, S, SO, S02, or SO2NH2 and R 12 is hydrogen or a group R1 as defined above;
or a group R'RN where R' and R@ are as defined above, with the proviso that any hetero atom substituent in R1 and/or W must be separated from the aromatic hetero atom substituent by at least two carbon atoms (preferably saturated).

In the compounds of formula (11).

13 13
R1 preferably represents phenyl substituted by a group selected from OR , -COR C02R 13, SOR 13, S02R 13@ CONRI3 R 14 @ NR 14C(O)NR". Cl-loalkyl, CI-10alkoxy, haloCI-10alkyl, aryl, aryl Ci-joalkyl, heteroaryl or heteroaryl Cl-loalkyl; wherein R13 and R14 each independently represents hydrogen, CI-10alkYl, C2-loalkenyl, C2-10alkYnYl.

C3-6cycloalkyl,
C3-6CYCloalkenyl, aryl, arylCl-loalkyl, heteroaryl, heteroarylCl-loalkyl, reduced heteroaryl or reduced heteroarylCl-loalkyl.

More preferably R1 represents phenyl substituted by OR 13 or COR 13 wherein R 13 is preferably aryl, most preferably phenyl; phenyl substituted by -CO2R 13 wherein R13 represents Cl-loalkyl, preferably CI-6alkyl; or phenyl substituted by C6-10alk-yl
R2 preferably represents hydrogen or CI-10alkyl;
R'@ R9@ R'0 and R" preferably each independently represents hydrogen, halo, hydroxy, amino, nitro, cyano, thiol, CI-10alkyl, Cl-loalkoxy3 Cl-locycloalkyl, Cl-locycloalkoxy,
16
C(O)R". C(O)NR"R , S(O)R" or haloCI-10alkyl;
where R15 and R 16 each independently represent hydrogen or C I - 1 oalkyl.

R8 is hydrogen or halogen e.g. fluorine; most preferably hydrogen;
R9 is preferably hydrogen or lower branched or unbranched alkyl having I to 10 carbon atoms: cyclic alkyl having 3 to 6 carbon atoms, e.g. cyclopropyl; haloCI-6alkyl,
e.g. trifluoromethyl; or a halogen, e.g. chlorine or fluorine;
R' 0 is preferably hydrogen, lower branched or unbranched alkyl having I to IO carbon atoms e.g. ethyl, butyl or octyl: cyclic alkyl having 3 to 6 carbon atoms, e.g.

cyclopropyl; haloCI-6alkyl, e.g. trifluoromethyl or a halogen, e.g. chlorine or fluorine; R' 1 is

preferably hydrogen, halogen, eg. fluorine; or branched or unbranched alkyl having I to IO carbon atoms.

8
Preferably, in compounds of formula (11) at least one of R., R9, R' 0 and R" represents a substituent other than hydrogen. Tbus, for example, R8 may represent a hydrogen atom and R9, R'0 and R" are as defined above. In a prefer-red embodiment each of R8 1 5 and R' 1 represents a hydrogen atom, and one or both of R9 and R'0 represents a substituent as defined above.

Preferably, a compound for use according- to the first aspect of the invention comprises a compound of formula (II) or a pharmaceutically acceptable salt, ester, amide or prodrug therof-, wherein.

R' is aryl e.g. optionally substituted phenyl or 2-naphthyl, or an aryl alkyl group wherein the alkyl moiety has up to 25 e.g. up to 20 carbon atoms, or an aryl aryl group; wherein the aryl alkyl group or the aryl aryl group may be separated by a spacer where the spacer can be an ester, amide, 0, CH2, or a ketone and wherein any aryl group is preferably a phenyl, optionally substituted with alkyl, haloalkyl or
halogen;
R2 is hydrogen or is a group as defined above for R'
PCT/GBOO/00032 R8 is hydrogen or fluorine;
R9 is lower branched or unbranched alkyl having I to IO carbon atoms; cyclic alkyl having 3 to IO carbon atoms, e.g. cyclopropyl; haloalkyl, e.g. trifluoromethyl; or a
halogen, e.g. chlorine or fluorine;
R10 is lower branched or unbranched alkyl having I to 10 carbon atoms; e.g. ethyl, butyl or octyl, cyclic alkyl having 3 to 10 carbon atoms, e.g. cyclopropyl; haloalkyl,
e.g. trifluoromethyl; or a halogen, e.g. chlorine or fluorine;
I 0
R1 1 is hydrogen, lower branched or unbranched alkyl having I to IO carbon atoms, or halogen, e.g. fluorine.

Most preferably, R' is unsubstituted phenyl or phenyl substituted by a group selected 1 5 from C 1 -8 alkyl, eg butyl, pentyl, hexyl or heptyl; halo-C 1 -8 alkyl, eg CF3; OR6 where R6 is phenyl or COW where W is phenyl or C I -8 alkyl.

In a second aspect the present invention provides novel compounds of formula (Ila).

R8a 0
R9
0
N Rla
R1
R11a R2a
(Ila)
or a pharmaceutically acceptable salt, ester, amide or prodrug therof;
wherein:
R la represents
(i) a C 10-3o branched or unbranched alkyl, C2.30 alkenyl, C2-30 alkynyl, cycloalkenyl, , aryl-CIO-30 alkyl, aryl-CIO-30 alkenyl, heteroaryl, heteroaryl-Cl.30 alkyl, heteroaryl-C2-30 alkenyl, reduced aryl, reduced heteroaryl, reduced heteroaryl-CI-30 alkyl or a substituted derivative therof wherein the

substituents are one or more independently chosen from the group consisting of halogen, CI-10 alkyl, halosubstituted CI-10 alkyl, aryl, aryl-CI-10 alkyl, heteroaryl, reduced heteroaryl, reduced heteroaryl-Cl-lo alkyl,
13 13 13 13 13 14
.NR R
aryl-Cl-lo alkoxy, cyano, nitro, -C(O)R 5-CO2R . -SOR -SO2R
13 13
C(O)NRII 14@
NR14C 13
OR 1, -SR 9 R and (O)R , with the proviso that any hetero atom
substituent in R1 must be separated from the exocyclic nitrogen atom by at least two carbon atoms (preferably saturated); or
(ii) aryl substituted by one or more independently chosen from the group consisting of halosubstituted Cl-lo alkyl, aryl, aryl-CI-10 alkyl, heteroaryl, reduced heteroaryl,
13 -CO2R 13 @ -SOR 13
reduced heteroaryl-Cl-lo alkyl, aryl-Cl-lo alkoxy, cyano, -C(O)R 5
13 13 14 -OR" (providing that in this instance R 13 does not represent aryl
S02R . -NR R ,
13
C(O)NRI3 14, -NR 14C 13
or alkyl), -SR. 5 R and (O)R
wherein:R 13 and R 14 each independently represents hydrogen, Cl-loalkyl, C2-10alkenyl, C2-loalkynyI5 C3-6CYCloalkyl,
C3-6CYCloalkenyl, aryl, mylCl-loalkyl, heteroaryl, heteroarylCl-loalkyl, reduced heteroaryl or reduced heteroarylCl-loalkyl;
2a is hydrogen or is a group as defined above for Rl; and
8a, R9a , RI Oa , R1 la are as defined above for formula (11).

provided that.

when RI represents a heteroaryl group it is not thiadiazolyl, triazolyl or thiazolyl and when RI represents a reduced heteroaryl group it is not thiazolidinyl.

In the compounds of formula (Ila).

Rla preferably represents phenyl substituted by a group selected from OR 13 (providing
13 13 13 13
in this instance R does not represent alkyl or aryl), -COR ,C02R". SOR S02R CONR 13R14 1 NR 14C(O)NR'3, haloC,-ioalkyl, aryl, aryl CI-10alkyl, heteroaryl or heteroaryl CI-10alkyl.

More preferably RI' represents phenyl substitued by COR 13 wherein R 13 is preferably aryl, most preferably phenyl; or phenyl substituted by -CO2RI3 wherein RI3represents CI-10alkyl, preferably CI-6alkyl.

1 5 R2' preferably represents hydrogen or C I., oalkyl;
R8a, R9a , RI Oa and RI la preferably each independently represents hydrogen, halo, hydroxy, amino, nitro, cyano, thiol, CI-10alkyl, Cl-joalkoxy@ Cl-locycloalkyl, Cl
15 16
locycloalkoxy, C(O)R , C(O)NR"R , S(O)R4a or haloCI-10alkyl;

where R15 and R16 each independently represent hydrogen or Cl-loalkyl.

R8' is hydrogen or halogen e.g. fluorine; most preferably hydrogen;
Wa is preferably hydrogen or lower branched or unbranched alkyl having 1 to IO carbon atoms; cyclic alkyl having 3 to 6 carbon atoms; e.g. cyclopropyl, haloCI-6alkyl,
e.g. trifluoromethyl or a halogen, e.g. chlorine or fluorine;
R10' is more preferably hydrogen, lower branched or unbranched alkyl having I to IO carbon atoms e.g. ethyl, butyl or octyl; cyclic alkyl having 3 to 6 carbon atoms e.g.

cyclopropyl, haloCI-6alkyl e.g. trifluoromethyl or a halogen e.g. chlorine or fluorine; Rl " is preferably hydrogen, halogen, eg. fluorine; or branched or unbranched alkyl having I to 1 0 carbon atoms.

8a a Oa la
Preferably, in compounds of formula (11a) at least one of R ,R9, Rl and Rl represents a substituent other than hydrogen. Thus, for example, R8, may represent a
hydrogen atom and R 9a , Rl Oa andR'Iaareasdefinedabove. Inaprefeffed
embodiment each of R 8a and Rl la represents a hydrogen atom, and one or both of R9a and Rl Oa represents a substituent as defined above.

In a yet further embodiment the present invention provides compounds of formula
(lIb)
R8 0
R9
0
20
R1
R11
wherein
R8-Rl 1 are as defined hereinbefore and
R@O represents C 1-2oalkyl, C 1-20alkoxy, or optionally substituted phenoxy.

Preferred substituents for phenoxy include one or more of halo, CF3, lower alkyl and lower alkoxy groups.

When R20 represents an alkyl or alkoxy group this preferably contains from 6-12 carbon atoms.

In this embodiment WO is most preferably phenoxy.

Preferred values of R8 - R" are as defined above.

Compounds of formula (Ilb) represent a novel selection on the basis of their advantageous activity as lipase inhibitors.

I 0
Examples of pharmaceutically acceptable salts of the formula include those derived from organic acids such as methanesulphonic acid, benzenesulphonic acid and ptoluenesulphonic acid, mineral acids such as hydrochloric and sulphuric acid and the
like, giving methanesulphonate, benzenesulphonate, p-toluenesulphonate,
1 5 hydrochloride and sulphate, and the like, respectively or those derived from bases such as

organic and inorganic bases. Examples of suitable inorganic bases for the formation of salts of compounds for this invention include the hydroxides, carbonates, and bicarbonates of ammonia, lithium, sodium, calcium, potassium, aluminium, magnesium, zinc and the like. Salts can also be formed with suitable organic bases.

Such bases suitable for the formation of pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases which are nontoxic and strong enough to form salts. Such organic bases are already well known in the art and may include amino acids such as arginine and lysine, mono-, di-, or trihydroxyalkylamines such as mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and trimethylamine, guanidine; N-methylglucosamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl) aminomethane; and the like.

Salts may be prepared in a conventional manner using methods well known in the art.

Acid addition salts of said basic compounds may be prepared by dissolving the free 16 PCT/GBOO/00032 base compounds according to the first or second aspects of the invention in aqueous or aqueous alcohol solution or other suitable solvents containing the required acid. Where a compound of formula (1) contains an acidic function a base salt of said compound may be prepared by reacting said compound with a suitable base. The acid or base salt may separate directly or can be obtained by concentrating the solution eg. by evaporation. The compounds of this invention may also exist in solvated or hydrated forms.

The invention also extends to prodrugs of the aforementioned compounds. A prodrug I 0 is commonly described as an inactive or protected derivative of an active ingredient or a drug which is converted to the active ingredient or drug in the body.

Representative compounds according to the first and /or second aspects of the invention are those which include;
1 5
Table 1
Reference
Number Structure Compound Name
0 2-Phenylamino-4H-3,1
I benzoxazin one
NJO
H
2
2-(4-Butylphenylamino)-4H
0 3,1-benzoxazin one
N
H
17 PCT/GBOO/00032
0 6-Chloro phenylamino4H
cl 3, 1 -benzoxazin one
N
H
4
0 2-Butylamino-4H-3,1

benzoxazin one
H
5 0
Me J@o 6-Methyl phenylamino-4H
3 benzoxazin one
N;@@N"O
H
6
0 2-(4-Methoxyphenylamino)
ow 4H-3, I -benzoxazin one
C WIN
H
7 0
2-(4-Methylphenylamino)
4H-3, I -benzoxazin one
CC'N@:%'Cr
H
8 0
0 2-(4-Phenoxyphenylamino)
4H-3,1 -benzoxazin one
N"- N
H
9 0
cl 2-(4-Chlorophenylamino)-4H
3, 1 -benzoxazin one
N. 1@ Ni::::r
H
18 PCT/GBOO/00032 I 0
2-[4(l -Methylethyl)
0 phenylamino]-4H-3,1
C] benzoxazin one
H
0
CF3 2-(4
Trifluoromethylphenylamino)
W'Z Nj::x -4H-3,1-benzoxazin one
H
1 2 0
2-(3-Trifluoromethyl
phenylamino)-4H-3,1
N@:@ N CF3 benzoxazin one
H
1 3 0
6-Methyl (naphth
ylaniino)-4H-3,1-benzoxazin
kN kN
4-one
1 4
0 2-(4-Butoxycarbonyl
phenylamino) methyl-4H

3,1-benzoxazin one
H
1 5
0 6-Methyl (4-phenoxy
Me 0 phenylamino)-4H-3,1
N benzoxazin one
H
1 6 0
2-Ethylamino-4H-3,1
benzoxazin one
H
19 PCT/GBOO/00032 0 7-Fluoro phenylamino-4H
3, 1 -benzoxazin one
0
F
1 8 F 0 5-Fluoro phenylamino-4H
3, 1 -benzoxazin one
1 9 0 7-Methyl phenylamino-4H
3,1-benzoxazin one
Me,"'@ N"
20 0 7-Ethyl Phenylamino-4H
3, 1 -benzoxazin one
N.e@o
H
2 1 0 2-(4-Hexylphenylamino)
methyl-4H-3,1-benzoxazin
one
WIN
H
22 2-(4-Heptyloxyphenylamino)0 6-methyl-4H-3,1 -benzoxazin
4-one
N4NI@a
H
23 7-Octyl phenylamino-4H
3, 1 -benzoxazin one
0
N-::@ N
H
24 0 7-Methyl (4-phenoxy
phenylamino)-4H-3,1
0 benzoxazin one
N;@ N
H
2-Hexadecylamino methyl
4H-3,1 -benzoxazin one
0
@@eNIIN
H
26 7-Butyl phenylamino-4H

0 3, 1 -benzoxazin one
0
N N`@O
H
27 0 7-Methyl (2phenoxyphenylamino)-4H
3,1 -benzoxazin one
N'5@@o N
H 0
28 0 7-Methyl (3phenoxyphenylamino)-4H
3,1 -benzoxazin one
N N
H
29 2-(4-Benzoylphenylamino)
methyl-4H-3, I -benzoxazin
one
0
N N
H
2-(4-Phenoxyphenylamino)
0 trifluoromethyl-4H 1.

I benzoxazin one
N
F3 H
31 7-Methyl (4octylphenylarnino)-4H-3, I
0 benzoxazin one
H
3 2 0 2-Phenylamino-4H
pyrido[3,4-d][1,3]oxazin
one
H
3 3 0 2-(2-Cyanophenylamino)
methyl-4H-3,1 -benzoxazin
one
W@
H
CN
34 6-Nitro phenylamino-4H
0 3, 1 -benzoxazin one
02 0
N N
H
3 5 6-Acetatnido phenylamino
H 0 4H-3, I -benzoxazin one
N
H
2-Phenylamino
0 trifluoromethyl-4H-3, I
benzoxazin one
F3C@@ WIW@C

H
3 7 0 7-Amino phenylamino-4H
3, 1 -benzoxazin one
0
H2N N"a
H
3 8 0 2-Phenylamino-4H
pyrido [2,3 -d] [1,3]oxazin
one
N'!@ N
H
39 2-Cyclopropylamino-4H-3,1
0 benzoxazin one
Wet NA
H
40 2-(3-Cyanophenylamino)
0 methyl-4H-3, 1 -benzoxazin
one
N-IeNj
H CN
4 1 0 2-(4-Cyanophenylaniino)-4H
CN 3, 1 -benzoxazin one
N'I@ W@@
H
CN 2-(4-Cyanophenylamino)
0 methyl-4H-3,1 -benzoxazin
one
ooo@,@@N N
H
0 2-(4-Carboxyphenylamino)
COOH 4H-3,1 -benzoxazin one
N'I@N
H
2-(4-Aminophenylamino)-4H
0 NH 3,1-benzoxazin one
N`@Z N
H
0 2-(4-Hydroxyphenylamino)
OH 4H-3,1 -benzoxazin one
WIN
H
2-(4-N
0 CONHMe Methylcarbainoylphenylamin
o)-4H-3,1-benzoxazin one
C N- N
H
2,2'-(1,8-Octylidenediamino)
0 bis-4H-3,1 -benzoxazin one
H

N
H y
O"IreAz@@
0
0 2-(2-Phenoxyphenylamino)
4H-3 5 1 -benzoxazin one
N
H
OPh
2-(3-phenoxyphenylamino).

4H-31 I -benzoxazin one
N-I@N OPh
H
50
0 2-(Naphth ylamino)-4H
3, 1 -benzoxazin one
(:@N N
H
5 1
0 2-(6-Phenylhexylamino)-4H.

3,1-benzoxazin one
H
52
0 2-(Pyrrol-3 -ylamino)-4H-3, I.

C@ @Nole N oooCN H benzoxazin one
H
5 3
0 2-(Piperidin ylatnino)-4H
3 9 I -benzoxazin one
ooeoH
C Wet N
H
54
0 2-[6-(Pyrrol yl)hexylaminol-4H 1
benzoxazin one
Cl N-1
H
0 2-(4-Ethoxycarbonyl
COOEt
phenylamino)-4H 1
benzoxazin one
N". N
H
56 0
NC 6-Cyano phenylamino-4H
3,1-benzoxazin one
H

57
2-Phenyl Trifluoromethyl
0 4H-3, I -benzoxazin one
F3C 0
N'f
H
5 8 0
HOCNN., 6-Formyl phenylamino-4H.

3,1 -benzoxazin one
N
H
59 0
H 02 s 2-Phenylamino-4H-3,1
0 benzoxazin one sulfinic
N N'j acid
H
60
0
7-Hydroxy phenylamino.

4H-3,1 -benzoxazin one
HO)C) Nj-@W@o
H
6 1 0
0 7-Cyclopropyl
I :::) phenylamino-4H-3,1
N `@ t@o benzoxazin one
H
PCT/GBOO/00032 0
6,7-Di.tnethyl phenylamino
4H-3,1 -benzoxazin one
N'I@W@a
H
0
6-lodo octylamino-4H-3, I
benzoxazin one
H
0 7-Butyl octylamino-4H-3, I
ko benzoxazin one
H
6-Methyl (dodeca
0 ynylamino)-4H-3,1
benzoxazin one
H
0 6-Methyl [6-(thien
yl)hexylainino]-4H-3,1
benzoxazin one
N" N

H
0 8-Fluoro phenylamino-4H
O 3,1-benzoxazin one
N-;@@ N
F H
0
6-Cyclopropyl
phenylamino-4H-3,1
benzoxazin one
H
HS--@, 6-Mercapto phenylamino
4H-3, I -benzoxazin one
Nl@ N----@O
H
70 0
NC 6-Cyano phenylamino-4H
3,1 -benzoxazin one
N
H
Compounds 2, 3, 5, 6, 8, 11-15 and 17-70 in Table I above are believed to be novel and as such represent preferred embodiments of the present invention.

Preferred compounds of formula (11) listed in Table I include compounds 1, 3, 5, 9, 17, 19, 20, 23 and 26.

Preferred compounds of formula (Ila) listed in Table I include compounds I 1, 12, 14, 25, 29 and 30.

Preferred compounds of formula (Ilb) listed in Table I include compounds 2, 6, 7, 8, 109 15@ 21@ 24.

Particularly preferred compounds of formula (Ila) and (Ilb) are.

2-(4-Phenoxyphenylamino)-4H-3,1 -benzoxazin one
2-(4-Butoxycarbonylphenylamino) methyl-4H-3, 1 -benzoxazin one
6-Methyl (4-phenoxyphenylarnino)-4H-3,1 -benzoxazin one
2-(4-Hexylphenylamino) methyl-4H-3, I -benzoxazin one
7-Methyl (4-phenoxyphenylamino)-4H-3,1 -benzoxazin one
2-(4-Benzoylphenylamino) methyl-4H-3, I -benzoxazin one
2-(4-Phenoxyphenylamino) trifluoromethyl-4H-3,1 -benzoxazin one
PCT/GBOO/00032 Preferred compounds of the invention listed above extend to the tautomers thereof, as well as (but not limited to) pharmaceutically acceptable salts, esters, amides or prodrugs thereof or a derivative with one or more lipid groups (natural or synthetic) attached.

A third aspect of the invention provides a process for the manufacture of any one or more of the novel compounds or derivatives according to the first and/or second aspects of the invention. Thus, the present invention provides a process for the preparation of a novel compound of formula (11) in particular a compound of formula I 0 (Ila) which process comprises.

Process (A) cyclising a compound of formula (III)
R8

R9 02R18
0
Rio 11
N'*@@ C- N R, R2
R11
wherein R' and Rs-R11 are as hereinbefore defined and R18 is hydrogen or C1-6alkyl.

or.

Process (B) reacting a compound of formula (IV)
R8 0
R9
R 0 (IV)
H
R11
PCT/GBOO/00032 with an amine of formula (V)
RWNH M
or.

Process (C) converting a compound of formula (1), (11), (Ila) or (lIb) into a different compound of formula (Ila) or (lIb), by, for example,
(i) reduction of a compound of formula (1), (11), (Ila) or (IIb) wherein any of R', R5 R?@ R'O and R" contains an alkenyl or alkynyl group or moiety, to the corresponding alkyl or alkenyl group or moiety; or
(fi) alkylation of a compound of formula (1), (II), (Ila) or (Ilb) where one or 1 5 more of R8, R?, R10 and R' 1 represents a halogen atom.

Process (A) may be effected by reacting a compound (III) with a dehydrating agent in an organic solvent. Suitable dehydrating agents include sulphuric acid, and when R" is hydrogen, 1-(3-dimethylaminopropyl) ethylcarbodiimide hydrochloride (EDC) or polymer supported EDC. The reaction may be effected at a temperature in the range to 50'C, preferably ambient temperature e.g. 20-30'C. When polymer supported EDC is employed it may be removed by filtration at the end of the reaction, and the product isolated from solution by standard procedures, such as removal of the solvent and purification by flash column chromatography. Alternatively the cyclisation may be effected using concentrated sulphuric acid.

Alternatively, cyclisation according to process (A) may be effected by reaction with excess chloroformate or by addition of another cyclisation reagent, which promotes ring closure. Suitable cyclisation reagents include for example, methyl chlorofonnate, carbonyl diimidazole, acetic anhydride, phosgene, oxalyl chloride, thionyl chloride or a peptide coupling agent such as dicyclohexyl carbodiimide (DCQ. The cyclisation reagent is preferably phosgene, triphosgene or thionyl chloride. When a chloroformate is employed this is preferably a low molecular weight chloroform@te, on grounds of cost and ease of removing the resulting alcohol.

Compounds of the formula (III) may themselves be prepared according to a variety of methods. Thus for example a compound of formula.

R8

R9
C02R18
NH (VI)
R10 2
R11
1 5 can be reacted with an isocyanate of formula (VII).

0 = C = N - R' (VII)
The reaction is preferably carried out in an inert organic solvent, such as an ether e.g.

tetrahydrofuran, an aliphatic hydrocarbon such as pentane or hexane; a halogenated hydrocarbon such as dichloromethane; or an aromatic hydrocarbon such as benzene or toluene, and usually at ambient temperature. The intermediate urea may cyclise directly in a 'one pot' reaction, without isolation. Alternatively, if desired the urea may be isolated prior to cyclisation. Similarly any unreacted urea intermediate may be cyclised in a subsequent reaction step. It will be appreciated that the above reaction results in a compound (III) where R@ is hydrogen.

Alternatively a compound of formula (III) may be prepared by reacting an isocyanate of formula (VIII).

R8
0 R
R9 2 18 (Vill)
R1 ==C=O
R11
(wherein R', R95 R'O, R' 1 and R18 are as hereinbefore defined)
with an amine of formula (V) R'WNH.

Compounds of formula (111) may also be prepared from compounds of formula (IX)
R8
1 5 0 R
R9 2 18 (IX)
R1 NHCOCI
R1 1
by reaction with an amine R1R2NH.

Compounds (IX) may themselves be prepared by reacting a compound (VI) with an amine (V) in the presence of trichloromethyl chloroformate and in a solvent such as tetrahydrofuran or dimethyl formamide.

Process (B) may be effected by reacting a compound of formula (IV) with an amine R1WNH in the presence of a base e.g. sodium hydroxide, followed by cyclisation, for example as described for process (A).

Compounds of formula (IV) may be obtained by cyclisation of a compound of formula (VI) wherein R18 is hydrogen using for example phosgene or a synthetic equivalent.

In process (C), reduction of an alkenyl or alkynyl group may be effected for example by catalytic hydrogenation using e.g. I 0% palladium on charcoal in an alcoholic solvent, such as ethanol, under I atmosphere of hydrogen gas.

Alkylation according to process (C)(ii) may be effected using a Stille or other palladium catalysed cross-coupling process, using e.g. tetra-alkyl tin such as tetrainethyl tin and PhCH2Pd(PPh3)2CI in HMPA at elevated temperature e.g. 501 OO'C. Other halides or pseudohalides e.g. triflates may be employed as starting materials.

I 0
Further methodology for preparing 2-amino- 1,3 -benzoxazin one derivatives is described in J Med Chem. 1990, 33(2):464-479 and J Med Chem. 1998 41:10601067, as well as US Patent No. 4,657,893.

1 5 A fourth aspect of the invention is a compound according to the first and/or second aspects of the invention (i.e. compounds of formulae (1), (II) and (Ila)), for use in medicine. Preferred features of the first and second aspects of the invention also apply to the fourth aspect. Further details of the fourth aspect of the invention are set out in the text which follows.

A fifth aspect of the invention relates to a compound according to the first and/or second aspects of the invention for use in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester ftinctionality. This includes both in vivo and in vitro uses and other uses such as industrial uses. Such an enzyme is one which catalyses the breakdown of a substrate containing an ester functionality by the addition of water, resulting in the cleavage of a chem ical bond. Such enzymes are involved in key processes in the body. Enzymes according to this invention include lipases (hydrolyse fatty acid esters), esterases (hydrolyse esters) and phosphatases (hydrolyse phosphate esters).

The enzyme is preferably a lipase. Lipases include pancreatic lipase, gastric lipase, lipoprotein lipase, lingual lipase, adipose tissue lipase, hormone sensitive lipase, phospholipase AI, A2, B, C, D etc., hepatic lipase, and other triacyl, diacyl and monoacylglycerol lipases in the mammalian body. Many similar such lipases are also known in plants, fungi and microorganisms.

Also covered are esterase enzymes and phosphatase enzymes. Esterase enzymes include pig liver esterase, cholesteryl esterase, retinyl esterase, 1 -alkyl glycerophosphocholine esterase, carboxylic ester hydrolases and cholesterol esterase.

I 0 Phosphatase enzymes include serine/threonine phosphatases PP1. PP2 and PP3, phosphoprotein phosphatase, myosin-light-chain phosphatase, protein phosphatase 2C and protein tyrosine phosphatase.

Compounds according to the invention, for use "in medicine, are primarily for use in 1 5 relation to the prevention and/or treatment of a medical condition such as obesity, hyperlipaemia, hyperlipidaemia and related diseases such as hyperglycaemia (type 11 diabetes), hypertension, cardiovascular disease, stroke, gastrointestinal disease and gastrointestinal conditions. Compounds according to the first and/or second aspects of the invention are useful in these and other conditions due to their ability to inhibit an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester functionality. The invention also relates to non-medical weight loss, such as cosmetic weight loss and includes improving bodily appearance in general. Throughout this text, the prevention and/or treatment of any disorder means any effect which mitigates any damage or any medical disorder, to any extent, and includes prevention and treatment themselves. The term "treatment" means any amelioration of disorder, disease, syndrome, condition, pain or a combination

of two or more thereof.

Clearly, an important application of the invention is in relation to weight loss (of all kinds as described above) in humans. However, the invention applies to medical and non-medical weight loss in any animal whose metabolism of fat and fat derivatives involves an enzyme whose preferred mode of action is to catalyse the hydrolysis of an, ester ftinctionality. Thus, the invention has veterinary application and is particularly useful in relation to medical and non-medical weight loss in companion animals such as pet cats and dogs as well as in animals which provide meat for human consumption.

In the case of the latter, the application of the present invention is to reduce fat content in order to provide a leaner meat product.

It is also believed that the compounds may be useful in reducing levels of toxins (e.g.

dioxins and PCBs) stored in body fat. Without wishing to be bound by theory, it is believed that increasing the amount of undigested fat passing through the body enhances diff-usion of toxins from fat stored in the body into fats in the blood, and thence into the intestine.

The fifth aspect of the invention has important applications. It includes test and diagnostic methods and the control and inhibition of unwanted enzymes, preferably lipases, in any process or in any product. The processes or products which preferably involve a lipase include processing of agricultural commodities (e.g. oilseeds), recovery and isolation of enzymes from biotechnological processes (e.g. involving lysis of microorganisms), the manufacture and extraction of crude oil (especially oil and plastics), the industrial manufacture of triglycerides or other fats, manufacture of healthcare goods which comprise surfactants, soap or detergent (e.g. bath oils, creams), the manufacturing and processing of liposomes (e.g. healthcare products, diagnostics, gene therapy), the treatment of industrial waste (e.g. paper effluent treatment) and preventing the degradation of foodstuff which comprises a fat (e.g.

chocolate processing). Thus, the invention also relates to these products and processes, eg. a foodstuff which comprises a compound according to the first aspect of the invention, in particular foodstuffs which have a high fat content such as cakes, biscuits, pastry-products and the like and chocolate products. The preferred features of the fifth aspect of the invention, including the preferred enzymes are as discussed for the previous aspects of the invention.

A sixth aspect of the invention provides a composition comprising a novel compound according to the first and second aspects of the invention, in combination with a pharmaceutically acceptable carrier or diluent. Suitable carriers and/or diluents are well known in the art and include pharmaceutical grade starch, mannitol, lactose, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose (or other sugar), magnesium carbonate, gelatin, oil, alcohol, detergents, emulsifiers or water (preferably sterile). The composition may be a mixed preparation of a composition or may be a combined preparation for simultaneous, separate or sequential use (including I 0 administration).

The compounds according to the invention for use in the aforementioned indications may be administered by any convenient method, for example by oral (including by inhalation), parenteral, mucosal (e.g. buccal, sublingual, nasal), rectal or transdermal 1 5 administration and the compositions adapted accordingly.

For oral administration, the compounds can be formulated as liquids or solids, for example solutions, syrups, suspensions or emulsions, tablets, capsules and lozenges.

20. A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable aqueous or non-aqueous liquid carrier(s) for example water, ethanol, glycerine, polyethylene glycol or an oil.

The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and microcrystalline cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, powders, granules or pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer I 0 coating of the formulation on a tablet or capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or non-aqueous or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, 1 5 lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or oral administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. . The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal or vaginal administration are conveniently in the form of suppositories (containing a conventional suppository base such as cocoa butter), pessaries, vaginal tabs, foams or enemas.

Compositions suitable for transdermal administration include ointments, gels and I 0 patches, and injections, including powder injections.

Conveniently the composition is in unit dose form such as a tablet, capsule or ampoule.

1 5 The compositions of the sixth aspect of the invention are useful in the prevention and/or treatment of obesity, obesity-related disorder, other medical weight loss and non-medical related weight loss. Preferred features of this aspect of the invention are as described above for the first to fifffi aspects of the invention.

A seventh aspect of the invention provides a process for the manufacture of a composition according to the sixth aspect of the invention. The manufacture can be carried out by standard techniques well known in the art and involves combining a compound according to the first or second aspect of the invention and the pharmaceutically acceptable carrier or diluent. The composition may be in any form including a tablet, a liquid, a capsule, and a powder or in the form of a food product, e.g. a functional food. In the latter case the food product itself may act as the pharmaceutically acceptable carrier.

An eighth aspect of the invention provides a method for the prevention and/or treatment of obesity or an obesity-related disorder, the method comprising the administration of a compound according to the first or second aspect of the invention, preferably in combination with a phannaceutically acceptable carrier or diluent (as per the sixth aspect of the invention). Obesity-related disorders include hyperlipeamia, hyperlipideamia, hyperglycaemia, hypertension, cardiovascular disease, stroke, gastrointestinal disease and gastrointestinal conditions. The compound or composition is preferably administered to a patient in need thereof and in a quantity sufficient to prevent and/or treat the symptoms of the condition, disorder or disease. For all aspects of the invention, particularly medical ones, the administration of a compound or composition has a dosage regime which will ultimately be determined by the attending I 0 physician and will take into consideration such factors such as the compound being used, animal type, age, weight, severity of symptoms, method of administration, adverse reactions and/or other contraindications. Specific defined dosage ranges can be determined by standard design clinical trials with patient progress and recovery being fully monitored. Such trials may use an escalating dose design using a low 1 5 percentage of the maximum tolerated dose in animals as the starting dose in man.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between I mg and 2000 mg, preferably between 30 mg and 1000 mg, e.g.

between IO and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0. I mg and I 00 mg, preferably between 0. I mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered I to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

A ninth aspect of the invention provides a cosmetic method for maintaining a given weight, or for cosmetic weight loss, the method comprising the administration of a compound according to the first aspect of the invention, preferably in combination with a pharmaceutically acceptable carrier or diluent (as per the fifth aspect of the invention). The "medicament" is preferably administered to a patientin need thereof and in a quantity sufficient to maintain a given weight or for cosmetic weight loss. The eighth and ninth aspects of the invention relate to methods of treatment of humans and other animals, in particular companion animals and other animals which provide meat for human consumption, such as cattle, pigs and sheep (all of any age).

The invention will now be described with reference to the following non-limiting I 0 examples.

Biological Test Methods and Results
Test Compounds
1 5 The benzoxazinone compounds used in the following tests are identified by the reference number assigned in Table I hereinbefore.

Measurement of lipase activily using a guinine dfimine dye colorimetric assay The inhibitory activity of the selected compounds to pancreatic lipase was measured in the following assay available from Sigma Ltd (Lipase PSTM, catalog number 805-A).

Pancreatic lipase
1,2-dibutyrin ---------- > 2-monoglyceride + fatty acid
Monoglyceride lipase
2-monoglyceride ---------- > glycerol + fatty acid
Glycerol kinase
glycerol + ATP ---------- > glycerol phosphate + ADP
Glycerol phosphate oxidase
glycerol phosphate + 02 ---------- > dihydroxyacetone phosphate + H202
Peroxidase
H202 + 4-AAP + TOOS ---------- > quinine diimine dye + 4H20
The glycerol released from the action of pancreatic and monoglyceride lipase was oxidised to release H202. The peroxidase reaction step then produces a quinine dye which is pink in colour and absorbs light at a wavelength of 550 mn.

Inhibitor
Individual compounds were dissolved in DMSO (dimethyl sulphoxide) at 10 MM.

DMSO was used to avoid any problems with compounds being water-insoluble.

For individual compounds, the IC50 (concentration at which lipase activity is inhibited to one half of the maximum) was calculated by measuring the inhibitory activity from log-dose response curves using a range of inhibitor concentrations.

Results
A range of compounds were assayed in the quinine diimine dye colorimetric assay which provides a rapid method to measure lipase inhibitory activity. None of the compounds tested interfered with the colorimetric reaction, i.e. they did not give false positive results.

A range of inhibitory activities for the tested benzoxazinone compounds were observed, indicating that these compounds are inhibitors of human pancreatic lipase. The following compounds had IC50'S < 1 PM: 1-3, 5-12, 14, 15, 17, 19-2 15
23-26@ 28
Measurement of lipase engyme activily using a NaOH fitration method
The inhibitory activity of the selected compounds to pancreatic lipase was measured in the assay described in Pasquier et al., 1986, Vol 7, Nutritional Biochemishy, 2931 0 302.

Log dose/response curves were constructed using a range of inhibitor concentrations.

Results
1 5
Selected benzoxazinone compounds were tested in the NaOH titration assay. In this assay, the activity of porcine pancreatic lipase in a system containing lipid micelles is recorded. These conditions are therefore similar to those encountered in the gastrointestinal tract.

A range of inhibitory activities were observed for the tested benzoxazinone compounds in this assay indicating that these compounds are inhibitors of porcine pancreatic lipase. The following compounds had an IC50 < 2@iM: 1-3, 5, 8, 11, 12, 14-205 24, 26@ 28@ 2% 30.

Thus, the results demonstrate that the tested benzoxazinones are inhibitors of fat digestion and that these compounds may be particularly suitable for the treatment of obesity.

Mouse Model Assgy
Compound 24 was assayed 'in a mouse model as described by Isler et al., British Journal offutrition, 1995, 73:851-862 and was found to be a potent lipase inhibitor.

Synthesis of Intermediates
I 0 Synthesis of 4-substituted anthranilic acids
Example: 4-octyl anthranilic acid (4-octyl aminobenzoic acid)
Method based on that of L.A. Paquette et al. J.Am.Chem.Soc. 99, 3734 (198 1)
Br Br
N02
A solution of I -bromo octylbenzene (9.9g, 3 6mmol) in sulfuric acid (20ml) was cooled in an ice bath. To this was added nitric acid (1.44ml, 36mmol). The ice bath was removed and the mixture stirred at room temperature for 20 minutes. A further portion of nitric acid was added (0.07ml, 1.75mmol), stirring being continued for a further 20 min. The mixture was poured into aqueous potassium carbonate, which was extracted with ethyl acetate. The organic extract was washed with saturated aqueous potassium carbonate, water and brine then dried (MgSO4) and concentrated.

Purification of the crude product by flash chromatography (I% EtOAc/hexane) removed the unwanted (major) regioisomer and afforded the desired material as a yellow oil (1.7g, 5.4mmol).

Br CN
The substrate (1.7g, 5.4mmol), copper (1) cyanide (0.533g, 5.9mmol) and pyridine (20ml) were refluxed at 150'C for 2 days. Concentration in vacuo and purification by flash chromatography (IO% to 20% EtOAc/hexane) gave the desired material as a
brown oil (739mg, 2.8mmol)
CN C02H
N02 N02
The substrate (694mg, 2.7mmol) was heated at 150'C in a mixture of water (2ml), AcOH (I ml) and sulfuric acid (I ml) for 2 days. The mixture was extracted with ethyl 1 5 acetate, the organic phase being washed with water (x 2), dried (Na2S04) and concentrated to give the desired material (744mg, 2.7mmol).

C02H C02H
11aNH2
The starting material (744mg, 2.7mmol) was dissolved in ethanol (10ml) and to this was added a

slurry of 1 0% palladium on charcoal (40mg) in ethanol (4ml). The flask was flushed with nitrogen then hydrogen (1 atni) after which stirring was maintained overnight. Further portions of catalyst (5mg and 25mg) were added, the reaction being complete after a further 24h. The reaction mixture was filtered through celite, thoroughly rinsing with methanol and ethyl acetate. Concentration gave the anthranilic acid (597mg, 2.4mmol) of sufficient purity for use without further purification; 8H (400 MHz, CDC13) 0 0.81 (3H, in, Me), 1 1.36 (10H, in, 5 x CHA1.52 (2H, br.s, ArCH2CH2), 2.45 (2H, br.s, ArCH2), 6.42 (2H, br.s, 2 x ArH), 7.74 (I H, br.s, ArH); m/z (ES) 250 (MH+).

Synthesis of substituted phenyl isocyanates
Example: Preparation of 4-octylphenyl isocyanate
OCN
A solution of 4-octylaniline (0.3 ml, 1.3 mmol) and diisopropylamine (0.205 ml, 5.2 mmol) in THIF (5 ml) was cooled to -1 O'C. A 20% solution of phosgene in toluene (1.3 ml, 2.6 mmol) was added, then the mixture was allowed to warm to r.t. and maintained at that temperature for 3h. Excess phosgene was removed under a stream of nitrogen (scrubbed on exit with NaOH(,,q)) to give a solution of the crude isocyanate, which was used directly in the next step.

4-Benzoylphenylisocyanate was prepared by an analogous procedure from the corresponding aniline.

Substituted 4-phenoxyphenyl isocyanates can be prepared from the corresponding amines by known procedures.

Synthesis of compounds according to the invention
ExMple I
Synthesis of 2-L4-Butoxycarbonyll2heUlamino) mELhyl-4H-3, I -benzoxazin one
(Reference number 14)
Me C02H Me C02HI
):::CNF12 + A,
UPC
A solution of 2-ainino methylbenzoic acid (690 mg, 4.57 mmol) in THF (2 ml) was treated with 4-n-butoxycarbonylphenyl isocyanate (1.0 g, 4.57 mmol). The mixture was kept at room temperature for 24 h, during which time the solvent was allowed to evaporate to leave a pale brown solid (1.7 g, quant.); 811 (400 MHz, DMSO-d6) 0.93
(3H5 t5 J 7. CH2CH3). 1.41 (2H, tq, J, J'7, CH2CHA 1.67 (2H@ tt, J@ J'7@
CH2CH2CHA 2.28 (3H, s, CHA 4.23 (2H, t, J 7, OCH2), 7.37 (IH, d, J 8, Ph),;7.77 (1 H, s, Ph), 7 7.92 (4H, in, Ph), 8.24 (I H5 d, J 8, Ph).

1 5
0 0
Mel,lj@@C02H PS-EDC me
10
N'k N-'@@@
H H H
To a solution of the urea (I 8 5 mg, 0. 5 mmol) in DMF (IO ml) was added polymersupported EDC (PS-EDC) (0.8 mmol g-1, 1.0 g). The resulting mixture was agitated at room temperature for 18 h, after which the resin was filtered off and washed with DMF (2 x 5 ml). The filtrate and washings were combined and evaporated under reduced pressure to afford the required compound as an off-

white solid (I 50 mg, 85%); 811 (400 MHz, DMSO-d6) 0.94 (3H, t, J7, CH2CHA 1.42 (2H5 tq, J, J'7, CH2CHA 1.69 (2H5 tt, J, J'7, CH2CH2CHA 2.3 9 (3H, s, CHA 4.25 (2H, t, J 7, OCHA 7.36 (IHI d@ J 8@ Ph)9 7.63 (IHI d5 J 8@ Ph)5 7.80 (lH, s, Ph),), 7 7.95 (4H, in, Ph); m1z (ES-) 351 (M-H+).

Exgmple 2
Synthesis of 6-Methyl (4-13henoxyl2heLiylamino)-4H-3,1-benzoxazin one
(Reference number 15)
Mel,aCO2H M
NH2
A solution of 2-amino methylbenzoic acid (I 72 mg, 1. IO mmol) in THF (I ml) was treated with 4-phenoxyphenyl isocyanate (241 mg, 1. I 0 mmol). The mixture was kept I 0 at room temperature for 24 h, during which time the solvent was allowed to evaporate to leave a pale brown solid. This was dissolved in DMF (5 nil) and added to a suspension of PS-EDC (0.8 mmol g-1, 2.8 g) in DMF (20 ml). The resulting mixture was agitated at room temperature for 18 h, after which the resin was filtered off and
washed with DMF (2 x 5 ml). The filtrate and washings were combined and
1 5 evaporated under reduced pressure. Flash column chromatography over silica (20% ethyl acetate in hexane as eluent) afforded the required compound as an off-white solid (I 53 mg, 40%); 5H (400 Nfflz, DMSO-d6) 2.36 (311, s, C113), 6.96 (211, d, J 8, Ph)@ 7.04 (ffl@ d9 J 89 Ph)5 7.09 (111@ t@ J 81 Ph)9 7.26 (111@ d@ J 8@ Ph), 7 7.38 (211. in.

Ph)@ 7 7.56 (111, in, Ph), 7 7.78 (411, in, Ph); nilz (ES+) 345 (N4H+).

Exg=le 3
2-(3-chlorophenvlamino) ociyl-4H-3,1 -benzoxazin one
C02H
NH2 N el
H
C02H
@@@@NH HN Cl
if
0
The anthranilic acid (200mg, 0.8 mmol) was dissolved in anhydrous THF (Iml), and to this was added 3-chlorophenylisocyanate (I 17gl, 0.96 mmol). The mixture was stiffed for 3h before being concentrated. The residue was partitioned between water and ethyl acetate. The organic layer was washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate and brine then dried (MgSO4) and concentrated to give an orange solid. This was purified by flash chromatography on silica (1 5% EtOAc/hexane to I 00% EtOAc, then IO% Et0H/Et0Ac) which gave, in order of elution, the I 0 benzoxazinone (18mg, 0.05 mmol); 811 (400 MHz, CDC13) 0 0.82 (3H, in, Me),
1..1 9 24 (I OH, in, 5 x CH2),1 1.57 (2H, in, ArCH2CH2), 2 2.62 (2H, m,
ArCH2). 7 7.32 (4H, in, 3 x ArH, NH), 7 7.49 (2H, in, 2 x ArH), 7 7.83 (2H, in, ArH); m/z (ES) 3 85 (MH+) and the urea (I 60mg, 0.4 mmol); m/z (ES@ 401 (MH)-.

1 5.
The residual urea may be cyclised in a separate step (as in the procedure below) to afford more benzoxazinone if required.

Example 4
7-0cjyI pheBylaniino-4H-3, I -benzoxazin one (coMound 23)

C02H
NHPh N-5@k NkPh
ir
0
The urea (126mg, 0.34 mmol) was suspended in dry DCM (4ml). 1-[3(Dimethylarnino)propyl] ethylcarbodiimide hydrochloride (EDC, 13 lmg, 0.68 mmol) was added and the mixture stirred for 24h. A further portion of EDC (I 3 1 mg, 0.68 mmol) was added and the mixture was stiffed for a further 24h. The mixture was diluted with ethyl acetate and washed with water, saturated aqueous sodium bicarbonate and brine, then driea (Na2SO4) and concentrated. This gave the desired benzoxazinone (89mg, 0.25 mmol), which did not require further purification: 8H (400 MIjz,. CDC13) 0.92 (3H, t, J 6.7, Me), 1 1.36 (10H, rn, 5 x CH2),1 1.70 (2H, rn, ArCH2CH2),2 2.75 (211, m, ArCI12), 6.80 (I H, br.s, NH), 7 7.21 (2H, m, 2 x Affl), 7.28 (111, s, Affl), 7 7.46 (211, m, ArH), 7.70 (211, d, J8.2, Arfl), 8.04 (I H, d, J 8. 1, Arfl); m/z (ES+) 3 51 (MH+).

Example 5
7-MeLhyl (4-phenoxvphenyl)-4H-3, I -benzoxazin one.

0 0
OH 0 H
I @@ 0
NH OCNjCr @@C NH
2
O-@@ N
H
2-Amino methylbenzoic acid (207 mg, 1.37 mmol) in THF (3 ml) was treated with 4-phenoxyphenyl isocyanate (289 mg, 1.37 mmol). The mixture was kept at M. for 48h then diluted with ethyl acetate and washed with 2N HCI, water, saturated aqueous sodium bicarbonate and brine, dried (Na2SO4) and concentrated. The residue was chromatographed on silica (50% to 100% ethyl acetate/hexane gradient, then 1% methanol/ethyl acetate) to give a white solid (217 mg, 0.6 mmol, 44%); 6H (400 MHz, DMSO-d6) 2.28 (3H, s, Me), 6.72 (I H, d, J 8.0, ArH), 6.95 (4H, m, ArH), 7.08 (I H, t, J 6.9, ArH), 7.3 6 (2H, t, J 7.9, Affl), 7.5 6 (211, d, J 8.7, ArH), 7.8 7 (I H, d, J 7.6, ArH), 8.11 (lH, s, ArH), 9.49 (lH, s, NH); m/z (ES-) 362 (M-H)-.

0
0
OH 0%
0
H
N @@' N
H
The urea (217 mg, 0.6 mmol) in DCM (4 ml) was treated with EDC (126mg, 0.66 mmol). After 24h and 48h, further portions of EDC were added (1 15 mg each, 0.6 mmol). The mixture was diluted with ethyl acetate and washed with water, saturated 1 5 aqueous sodium bicarbonate and brine then dried (Na2SO4) and concentrated to afford the benzoxazinone (137 mg, 0.4 mmol, 67%); 8H (400 MHz, CDC13) 2.37 (31-1, s, Me), 6.7 (11-1, br.s, NH), 6 7.05 (6H, m, Affl), 7.14 (11-1, s, Affl), 7.27 (21-1, t, J7.7, ArH), 7.54 (2H, d, J8.7, ArH), 7.89 (11-1, d, J8.1, ArH); m/z (ES) 345 (MH+).

The other compounds listed in Table 1 may be prepared in a similar manner to Examples I to 5 above. In particular the following compounds were prepared using the starting materials indicated.

Compound Starting material 1 Starting material 2
number
2 2-aminobenzoic acid 4-butylphenyl isocyanate
2-aminobenzoic acid 4-phenoxyphenyl isocyanate
10 2-aminobenzoic acid 4(1-methylethyl)phenyl isocyanate
I 1 2-aminobenzoic acid 4-trifluoromethylphenyl isocyanate
12 2-aminobenzoic acid 3-trifluoromethylphenyl isocyanate
13 2-amino methylbenzoic acid 1-naphthyl isocyanate
14 2-amino methylbenzoic acid 4-butoxycarbonylpheilyl isocyanate
1 5 2-amino methylbenzoic acid 4-phenoxyphenyl isocyanate
1 7 2-amino fluorobenzoic acid Phenyl isocyanate
1 8 2-amino fluorobenzoic acid Phenyl isocyanate
19 2-amino methylbenzoic acid Phenyl isocyanate
20 2-amino ethylbenzoic acid phenyl isocyanate
21 2-amino methylbenzoic acid 4-hexyl phenyl isocyanate
22 2-amino methylbenzoic acid 4-heptyloxyphenyl isocyanate
23 2-amino octylbenzoic acid Phenyl isocyanate
24 2-amino methylbenzoic acid 4-phenoxyphenyl isocyanate
25 2-amino methylbenzoic acid Hexadecylisocyanate
26 2-amino butylbenzoic acid phenyl isocyanate
27 2-amino methylbenzoic acid 2-phenoxyphenylisocyanate
28 2-amino methylbenzoic acid 3-phenoxyphenylisocyanate
29 2-ainino methylbenzoic acid 4-benzoylphenyl isocyanate
30 2-amino trifluoromethyl 4-phenoxyphenyl isocyanate
benzoic acid
3 I 2-amino methylbenzoic acid 4-octyl phenyl isocyanate
32 3-aminopyridine carboxylic Phenyl isocyanate
acid
33 2-amino methylbenzoic acid cyanophenyl isocyanate

The foregoing description details specific compounds, compositions, methods and uses which can be employed to practise the present invention. However, those skilled in the art will know how to use alternative reliable methods for aiming at alternative embodiments of the invention which are herein encompassed.

Claim

1 The use of a compound comprising formula (1):

0
0
R1
R2

or a pharmaceutically acceptable salt, ester, amide or prodrug therof; in the I 0 manufacture of a medicament for the prevention or treatment of conditions which require the inhibition of an enzyme whose preferred mode of action is to catalyse the
hydrolysis of an ester fimctionality;
wherein in formula (I):
5
A is a 6 membered aromatic or hetero-aromatic ring; and
R' is a branched or unbranched alkyl (optionally interrupted by one or more oxygen atoms), alkenyl,

alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, reduced aryl, reduced heteroaryl, reduced heteroarylalkyl or a substituted derivative therof wherein the substituents are one or more independently chosen from the group consisting of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, heteroaryl, reduced heteroaryl, reduced heteroarylalkyl, arylalkoxy, cyano, nitro, -C(O)W, -CO2W. -SOR4. -SO2R!, 6 -SR6, -C(O)CX'X2NR6R, -C(O)NWR', -C(O)N(OR')R6, -NR6C(O)W, NRR', -OR , -CR'(NH,)CO,R6, -NHCX'X'CO,R, -N(OH)C(O)NRR, -N(OH)C(O)W@ 6 NHC(O)NR6k7, -C(O)NHNRk7, -C(O)N(OR')R . or a lipid or steroid (natural or synthetic), with the proviso that any hetero atom substituent in R1 and/or R@ must-be separated from the exocyclic nitrogen atom by at least two carbon atoms (preferably saturated); and

R2 is hydrogen or is a group as defined above for R1;

and where:R@ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, reduced heteroaryl, reduced heteroarylalkyl, -OR, NHCX'X2CO2R6 or -NWR;

R5 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, reduced heteroaryl or reduced heteroarylalkyl; R6 and R7 are. independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, reduced heteroaryl, heteroarylalkyl, reduced heteroarylalkyl or -(CH2)n(OR5)m wherein n is I to 12, and

ra is 1-3; and

X1 and X2 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, reduced heteroaryl or reduced heteroarylalkyl.

---

2 Use according to claim I wherein the compound (I) is a compound of formula

R8 0
R9
0
ol@ N R 1
R10
R11 R2

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof,

wherein:

R', R@, R4, R', R@, R, X1 and X2 are as defined above for formula (I);

and

I 0

R'@ R?j R10, R1 1 are each independently hydrogen, halo, hydroxy, amino, nitro,. cyano, or a group R, as defined above;

1 5 or a group R12Q where Q is 0, CO, CONH, NHCO, S, SO, S02, or SO2NH2 and R 12 is hydrogen or a group R' as defined above;

or a group R'RN where R and R2 are as defined above, with the proviso that any hetero atom substituent in R1 and/or R@ must be separated from the aromatic hetero, atom substituent by at least two carbon atoms (preferably saturated).

3 Use according to claim 2 wherein in the compound of formula (II) R' is aryl or an aryl alkyl group wherein the alkyl moiety has up to 25 carbon atoms, or an aryl aryl group; wherein the aryl alkyl group or the aryl aryl group may be separated by a spacer where the spacer can be an ester, amide, 0, CH2, or a ketone;

R2 is hydrogen or is a group as defined above for R1;
R 8is hydrogen or fluorine;
R! is lower branched or unbranched alkyl having I to 1 0 carbon atoms; cyclic alkyl having 3 to 10 carbon atoms; haloalkyl; or a halogen;
0
R' 0 is lower branched or unbranched alkyl having I to 1 0 carbon atoms; cyclic alkyl having 3 to I 0 carbon atoms; haloalkyl; or a halogen;
R1 1 is hydrogen, lower branched or unbranched alkyl having 1 to IO carbon atoms, or 5 halogen.

4 Use according to any of claims I to 3 wherein R' represents phenyl substituted
13 13 13 13 13 14
by a group selected from OR , -COR ,C02R . SOR S02R , coNR13 R
14 13
NR C(O)NR , C@-joalkyl, CI-10alkoxy, haloCI-10alkyl, aryl, aryl CI-10alkyl, heteroaryl or heteroaryl CI-10alkyl; wherein R13 and R 14 each independently represents hydrogen, Cl-loalkyl, C2-loalkenyl, C2-joalkynyl, C3-6CYCloalkyl, C3-6cycloalkenyl, aryl, arylCijoalkyl, heteroaryl, heteroarylCl-loalkyl, reduced heteroaryl or reduced heteroarylCljoalkyl.

5 Use according to any of claims 1 to 4 wherein R1 represents phenyl substituted by OR 13 or COR 13 wherein R 13 is phenyl; phenyl substituted by -CO2R 13 wherein R13 represents C I - 1 oalkyl; or phenyl substituted by C6-1 0alkyl. 6 . Use according to any of claims 1 to 5 wherein the enzyme is a lipase. . Use according to any of claims I to 6 wherein said condition is selected from obesity, hyperlipaernia, hyperlipidaernia, hyperglycaemia (type II diabetes), hypertension, cardiovascular disease, stroke, gastrointestinal disease and gastrointestinal conditions.

8 Use according to any of claims I to 6 wherein said medicament is for reducing levels of toxins in body fat.

9 Use according to any of claims I to 8 wherein the medicament is f6r administration to humans.

10 Use according to any of claims I to 8 wherein the medicament is for administration to animals.

11 A compound of formula (Ha):
R8a 0
R9 0
N-@ N Rla
R1 R11a
R2a
(Ila)
or a pharmaceutically acceptable salt, ester, amide or prodrug therof;
wherein:
Riarepresents
(i) a CIO-30 branched or unbranched alkyl, C2-30 alkenyl, C2-30 alkynyl, cycloalkenyl, arYI-CIO-30 alkYl, arYI-CIO-30 alkenyl, heteroaryl, heteromyl-CI-30 alkyl, heteroUYI-C2-30 alkenyl, reduced aryl, reduced heteroaryl, reduced heteroaryl-CI-30 alkyl or a substituted derivative therof wherein the substituents are one or more independently chosen from the group consisting of halogen, CI-10 alkyl, halosubstituted CI-10 alkyl, aryl, aryl-CI-10 alkyl, heteroaryl, reduced heteroaryl,

reduced heteroaryl-Cl-lo alkyl,
13 13 13 13 13 14
aryl-CI-10 alkoxy, cyano, nitro, -C(O)R -CO2R , -SOR , -SO,R , -NR R
13 13
C(O)NRI3 14@ -NR 14C(O)R 13, with the proviso that any hetero atom
OR @ -SR 9 R and
substituent in Rl must be separated from the exocyclic nitrogen atom by at least two
carbon atoms (preferably saturated); or
I 0 (ii) aryl substituted by one or more independently chosen from the group consisting of
halosubstituted Cl-10 alkyl, aryl, aryl-CI-10 alkyl, heteroaryl, reduced heteroaryl,
13 13 -SOR 13
reduced heteroaryl-Cl-lo alkyl, aryl-Cl-lo alkoxy, cyano, -C(O)R I-CO2R @ 13 13 14 -OR 13
(providing that in this ins ce R13 does not represent aryl
-SO2R 5NR R @ tan
13 14
NR14 13
oralkyl),-SR",-C(O)NR R and C(O)R
wherein:R13 and R14 each independently represents hydrogen, Cl-lOaIkYl, C2-10alkenYl,
C2-loalkynyl, C3-6cycloalkyl,
C3-6CYCloalkenyl, aryl, mylCl-loalkyl, heteroaryl, heteroarylCl-loalkyl, reduced
heteroaryl or reduced heteroarylCl-loalkyl;
is hydrogen or is a group as defined above for Rl; and
R8a, R?a , Rl Oa , Rl I a are as defined above for R8@ R'@ R10 and R" in formula (11).
provided that:
when R" represents a heteroaryl group it is not thiadiazolyl, triazolyl or thiazolyl; and
la

when R represents a reduced heteroaryl group it is not thiazolidinyl. . A compound according to claim 1 1 wherein R la represents phenyl substituted by a group selected from OR 13 (providing in this instance R13 does not represent alkyl
or aryl), -COR 13, C02R 13@ SOR 13@ S02R 135 CONR"R 14 , NR 14C(O)NRII,
haloCl-loalkyl, aryl, aryl Cl-loalkyl, heteroaryl or heteroaryl. Cl-loalkyl.

13 A compound according to claim I I or claim 12 wherein R@a represents
hydrogen or Cl-loalkyl.

14 A compound according to any of claims 1 1 to 13 wherein R8a . R'a. R'0a and I 0 R1 I a each independently represents hydrogen, halo, hydroxy, amino, nitro, cyano, thiol, Cl-loalkyl@ Cl-loalkoxy@ Cl-locycloalkyl, Cl-locycloalkoxy, C(O)R"@ C(O)NR"R 16, S(O)R4a or haloCl-loalkyl; wherein R15 and R16 each independently represent hydrogen or Cl-loalkyl.

15 A compound of formula (IIb)
R8 0
R9
0 (11b)
20
R1 W@@ -@
H
R11
wherein
R 8-R1 1 are as defined hereinbefore and

R@o represents CI-2oalkyl, CI-20alkoxy, or optionally substituted phenoxy.

16 A compound of formula (II) selected from:
2-Phenylamino-4H-3,1 -benzoxazin one;
-Chloro phenylainino-4H-3, I -benzoxazin one;
2-Butylamino-4H-3,1-benzoxazin one;
6-Methyl phenylamino-4H-3,1-benzoxazin one;
2-(4-Chlorophenylamino)-4H-3,1-benzoxazin one;
6-Methyl (naphth ylamino)-4H-3, 1 -benzoxazin one;
2-Ethylwnino-4H-3,1 -benzoxazin one;
7-Fluoro phenylamino-4H-3, I -benzoxazin one;
5-Fluoro phenylamino-4H-3,1-benzoxazin one;
7-Methyl phenylamino-4H-3,1-benzoxazin one;
I 0 7-Ethyl Phenylamino-4H-3,1 -benzoxazin one;
7-Octyl phenylamino-4H-3,1 -benzoxazin one;
7-Butyl phenylamino-4H-3,1 -benzoxazin one;
2-Phenylamino-4H-pyrido[2,3-d][1,3]oxazin one;
6-Nitro phenylamino-4H-3,1-benzoxazin one;
1 5 6-Acetamido phenylamino-4H-3,1-benzoxazin one;
2-Phenylamino trifluoromethyl-4H-3,1-benzoxazin one;
7-Amino phenylamino-4H-3,1-benzoxazin one;
2-Phenylamino-4H-pyrido[3,4-d][1,3]oxazin one;
2-Cyclopropylamino-4H-3,1 -benzoxazin one;
2-(Naphth ylamino)-4H-3,1-benzoxazin one;
2-(6-Phenylhexylamino)-4H-3,I -benzoxazin one;
6-Cyano phenylamino-4H-3,1 -benzoxazin one;
6-Trifluoromethyl phenylamino-4H-3, 1 -benzoxazin one;
6-Formyl phenylamino-4H-3,1 -benzoxazin one;
2-Phenylamino-4H-3, I -benzoxazin one sulphinic acid;
7-Hydroxy phenylamino-4H-3,1 -benzoxazin one;
7-Cyclopropyl phenylamino-4H-3,1 -benzoxazin one;
6,7-Ditnethyl phenylamino-4H-3,1 -benzoxazin one;
6-lodo octylamino-4H-3, I -benzoxazin one;
3 0 7-Butyl octylamino-4H-3,1 -benzoxazin one;
6-Methyl (dodeca ynylamino)-4H-3,1 -benzoxazin one;
8-Fluoro phenylamino-4H-3,1-benzoxazin one;
6-Cyclopropyl phenyl-4H-3, I -benzoxazin one;
6-Mercapto phenylamino-4H-3,1 -benzoxazin one; and
3 5 6-Cyano phenylamino-4H-3,1-benzoxazin one;
or a salt, ester, amide or prodrug thereof

17 A compound of formula (Ila) selected from:
2-(4-Trifluoromethylphenylamino)-4H-3,1 -benzoxazin one;
2-(3-Trifluoromethylphenylamino)-4H-3,1-benzoxazin one;
2-(4-Butoxycarbonylphenylamino) methyl-4H-3, I -benzoxazin one;
-Hexadecylamino methyl-4H-3,1-benzoxazin one;
2-(4-Benzoylphenylamino) methyl-4H-3,1 -benzoxazin one;
2-(4-Phenoxyphenylamino) trifluoromethyl-4H-3,1-benzoxazin one;
2-(2-Cyanophenylarnino) methyl-4H-3,1-benzoxazin one;

2-(3-Cyanophenylamino) methyl-4H-3,1-benzoxazin one;
2-(4-Cyanophenylamino) methyl-4H-3,1-benzoxazin one;
2-(4-Cyanophenylatnino)-4H-3,1 -benzoxazin one;
2-(4-Carboxyphenylamino)-4H-3,1-benzoxazin one;
2-(4-Aminophenylamino)-4H-3, I -benzoxazin one;
1 0 2-(4-Hydroxyphenylamino)-4H-3,1-benzoxazin one;
2-(4-N-Methylcarbamoylphenylamino)-4H-3, I -benzoxazin one;
2,2'-(1,8-Octylidenediamino)-bis-4H-3,1-benzoxazin one;
2-(Pyrrol ylamino)-4H-3,1-benzoxazin one;
2-(Piperidin ylamino)-4H-3,1-benzoxazin one;
1 5 2-[6-(Pyrrol yl)-hexylamino]-4H-3,1 -benzoxazin one;
2-(4-Ethoxycarbonylphenylamino)-4H-3, I -benzoxazin one; and
6-Methyl [6-(thien yl)hexylamino]-4H-3,1 -benzoxazin one;
or a salt, ester, amide or prodrug thereof

18 A compound of formula (Ilb) selected from:
2-(4-Butylphenylamino)4H-3,1-benzoxazin one;
2-(4-Methoxyphenylamino)-4H-3,1 -benzoxazin one;
2-(4-Methylphenylamino)-4H-3, I -benzoxazin one;
2-(4-Phenoxyphenylainino)-4H-3,1 -benzoxazin one;
2-[4(l -Methylethyl)phenylamino]-4H-3, 1 -benzoxazin one;
6-Methyl (4-phenoxyphenylamino)-4H-3, I -benzoxazin one;
7-Ethyl Phenylamino-4H-3,1 -benzoxazin one;
2-(4-Hexylphenylamino) methyl-4H-3,1-benzoxazin one;
2-(4-Heptyloxyphenylamino) methyl-4H-3,1-benzoxazin one;
7-Methyl (4-phenoxyphenylaniino)-4H-3,1-benzoxazin one;
7-Methyl (2-phenoxyphenylamino)-4H-3,1-benzoxazin one;
7-Methyl (3-phenoxyphenylamino)-4H-3,1-benzoxazin one;
7-Methyl (4-octylphenylamino)-4H-3,1-benzoxazin one;
2-(2-Phenoxyphenylamino)-4H-3,1-benzoxazin one; and
2-(3-Phenoxyphenylamino)-4H-3, 1-benzoxazin one;
or a salt, ester, amide or prodrug thereof

19 A process for the preparation of a novel compound of formula (II) in particular a compound of formula (Ila) or formula Qlb) which process comprises:
Process (A) cyclising a compound of formula (III)
R8

5 0 R
R9 2 18
0
R10 11
N@@C-NR,R2
R11
wherein RI and R 8-R1 1 are as hereinbefore defined and R18 is hydrogen or C1-6alkyl.
or:
Process (B) reacting a compound of formula (IV)
R8 0
R9
0

N
R (IV)
R11
with an amine of formula (V)
R'R@NH M
or:
Process (C) converting a compound of formula (I), (11), (Ila) or (Ilb) into a different compound of formula (Ila) or (lIb), by, for example,
(i) reduction of a compound of formula (1), (II), (Ila) or (IIb) wherein any of R', R'5 R5 R' 0 and R1 1 contains an alkenyl or alkynyl group or moiety, to the corresponding alkyl or alkenyl group or moiety; or
(ii) alkylation of a compound of formula (1), (11), (Ila) or (IIb) where one or more of R8, R9, R10 and R" represents a halogen atom.

20 A compound, as claimed in any one of claims I I to 18, for use in medicine. I 0 21. A pharmaceutical composition comprising a novel compound of formula (II) or a pharmaceutically acceptable salt, ester, amide or pro-drug thereof, in combination with a pharmaceutically acceptable carrier or diluent.

22 A food product comprising a compound of formula (11) or a pharmaceutically 1 5 acceptable salt, ester, amide or pro-drug thereof.

23 A method for the prevention or treatment of obesity or an obesity related disorder, the method comprising administering a compound, as defined in any one of claims I to 18, or a composition as claimed in claim 21 or claim 22 to a patient.

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24 A compound, as defined in any one of claims I to 18, for use in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester fimctionality.

25 Use of a compound as defined in any of claims I to 18 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof to reduce fat content of animals which provide meat for human consumption. . A cosmetic method for maintaining a given weight, or for cosmetic weight loss, the method comprising the administration of a compound as defined in any of claims I to 18.

27 A compound comprising formula (I) hereinbefore described with reference to one or more of the examples.

28 A process for obtaining a compound comprising formula (1) hereinbefore described with reference to one or more of the examples.

29 The use of a compound comprising formula (1) in the inhibition of an enzyme whose preferred mode of action is to catalyse the hydrolysis of an ester ftmctionality hereinbefore described with reference to one or more of the examples.

30 Use according to claim 29 of a compound of formula (I) in the control and inhibition of unwated enzymes in a process or product.

31 Use according to claim 30 in the manufacture of healthcare goods comprising surfactants, soap or detergents.

32 Use according to claim 30 in preventing the degradation of foodstuff which comprises a fat.
INTERNATIONAL SEARCH REPORT

1 iational Application No
PCT/GB 00/00032
A. CLASSIFICATION OF S B11C1 MATTER
IPC 7 A61K317536 A61P3/04 C07D265/24 C07D498/04 C07D413/12
//(CO7D498/04,265:00,221:00)
According to International Patent Classification (IPC) or to both national classification and IPC
B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
C. DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.
X M. GOTSCHOW ET AL.: "Inhibition of 1-27
cathepsin G by 4H-3,1-benzoxazin ones"
BIOORGANIC & MEDICINAL CHEMISTRY,
vol. 5, no. 10, 1997, pages 1935-1942,
XPOO0904822
the whole document
X R.L. JARVEST ET AL.: "Inhibition of HSV-1 1-27
protease by benzoxazinones"
BICIORGANIC & MEDICINAL CHEMISTRY LETTERS,
vol. 6, no. 20, 1996, pages 2463-2466,
XPOO0904816
the whole document
X WO 96 37485 A (SEARLE & CO ;ABCOD NORMAN 1-27
(US); FLYNN DANIEL L (US); BECKER DANIEL)
28 November 1996 (1996 28)
claims
Further documents are listed in the continuation of box C. Patent family members are listed in annex.
A
o Special categories of cited documents
"T" later document published after the international filing date
"A" document defining the general state of the art which is not or priority date and not in conflict with the application but considered to be of particular relevance cited to understand the principle or theory underlying the
invention
"E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention
filing date cannot be considered novel or cannot be considered to
"L" document which may throw doubts on priority claim(s) or involve an inventive step when the document is taken alone which is cited to establish the publication date of another "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be

considered to involve an inventive step when the "O" document referring to an oral disclosure, use, exhibition or document is combined with one or more other such docu
other means ments, such combination being obvious to a person skilled
"P" document published prior to the international filing date but in the art. later than the priority date claimed 'A" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report
18 April 2000 28/04/2000
Name and mailing address of the ISA Authorized officer
European Patent Office, P.B. 581 8 Patentlaan 2
NIL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo M, Chouly, J
Fax: (+31-70) 340-3016
Form PCT/ISA/210 (second sheet) (July 1992)
page 1 of 2
INTERNATIONAL SEARCH REPORT
It iational Application No
PCT/GB 00/00032
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation of document, with indication,whero appropriate, of the relevant passages Relevant to claim No.
X WO 96 07648 A (WARNER LAMBERT CO) 1-27
14 March 1996 (1996 14)
claims
& US 5 652 237 A
cited in the application
X EP 0 147 211 A (SYNTEX INC) 1-27
3 July 1985 (1985 03)
claims
& US 4 657 893 A
cited in the application
X DE 23 15 303 A (BAYER AG) 1@19
17 October 1974 (1974 17)
cited in the application
claims
X US 3 450 700 A (ULRICH HENRI ET AL) 1-27
17 June 1969 (1969 17)
the whole document
Form PCT/ISA/21 0 (continuation of second shoot) (July 1992)
page 2 of 2
international application No.
INTERNATIONAL SEARCH REPORT PCT/GB 00/00032
Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) This International Search Report has not been established in respect of certain ciaims under Article 17(2)(a) for the following reasons:

1 F-X] Claims Nos.: 23@26
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 23,26
are directed to a method of treatment of the human/animal

body, the search has been carried out and based on the alleged
Claims Nos,: effects of the compound/composition.

2 FX 27-32
because they relate to parts of the international Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims 27-32 were not searched since they refer to any compounds,
formulations, processes and methods mentioned in the description;
therefore it does not comply with the requirements of the PCT, Rule 6.2a.

3 7 Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box 11 Observations where unity of invention is lacking (Continuation of item 2 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: I . As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2 As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4 F-1 No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos,: Remark on Protest F@ The additional search fees were accompanied by the applicant's protest. F-1 No protest accompanied the payment of additional search fees.
Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
INTERNATIONAL SEARCH REPORT
International Application No. PCT/tB 00 @00032
FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210
Continuation of Box I.2
Claims Nos.: 27-32
Claims 27-32 were not searched since they refer to any compounds,
formulations, processes and methods mentioned in the description;
therefore it does not comply with the requirements of the PCT, Rule 6.2a.
The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
INTERNATIONAL SEARCH REPORT
IiPCTiational Application No
Information on patent family members /GB 00/00032

Patent document Publication Patent family Publication
cited in search report date member(s) date

DE 2315303 A 17 1974 NONE

US 3450700 A 17 1969 NONE

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Form PCT/ISA/21 0 (patent family annex) (July 1992)